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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,473	09/09/2005	Ingrid Grummt	4121-177	2987

23448 7590 08/06/2007

INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
08/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,473	GRUMMT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *5-7,9,11-16,18,19 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,10,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on June 29, 2007 is acknowledged.

Applicant has elected the invention of Group I, claim(s) 1-10, 17 and 20, drawn to a pharmaceutical composition comprising a nucleic acid molecule encoding an inactive form of the human transcription initiation factor TIF-1A, and host cells comprising said nucleic acid molecule.

Within Group I, Applicant has elected the species:

i) wherein the TIF-IA mutation species is at position S649,

ii) wherein the cell type species is a mammalian cell, and

iii) wherein the recombinant vector species is a virus.

2. Election of Applicant's invention(s) was made with traverse.

With respect to the Restriction of Inventions, Applicant argues:

a) the International Preliminary Examination Report acknowledged the claims of Groups I-IV related to a single inventive concept, unified by their common special technical feature of a nucleic acid molecule encoding an inactive form of TIF-IA;

b) the subject matter of Groups III and IV are interrelated with Group I because the host cells and transgenic animals encompass the nucleic acid of Group I; and

c) the Group II method of treatment uses the product of Group I.

With respect to the species election requirement, Applicant argues the species possess a commonality of design, operation or effect, and therefore related to a single general inventive concept, specifically:

i) the TIF-IA species are all amino acid substitutions;

ii) the cell type species must be an adequate host for the vector, providing an adequate environment in which the vector can reproduce itself; and

iii) all vectors encompassed by the claims possess commonality of design, operation or effect.

Applicants' arguments have been fully considered but are not found persuasive.

With respect to a), the Examiner respectfully reminds Applicant that the International Preliminary Examination Report (March 17, 2005) acknowledged that Claim 21 "does not refer as all the other claims to the inactive, non-post-translationally modified TIF-IA. [I]t is possible that an objection of non-unity in reference to this claim may be raised in the regional phase." Thus, *a priori*, unity of invention is lacking.

With respect to b), the Examiner respectfully reminds Applicant that while the genus of recombinant host cells may be used in the method of producing a polypeptide, not all of the recombinant cells, e.g. insect cells, bacteria and yeast, and mammalian cell lines encompassed by Groups I and III are capable of generating the transgenic animal of Group IV. Furthermore, as claimed, the recombinant host cells of Group III require the mutation of S649; whereas, the Group IV transgenic animal is not required to comprise the same special technical feature, specifically a nucleic acid encoding a mutation of S649.

With respect to c), the Examiner is aware of the Group II method and the possible rejoinder upon allowability of the Group I product.

With respect to i), the claims embrace any amino acid substitution. However, Applicant is respectfully reminded that not all amino acid substitutions are the same. While S→A substitutions mimic loss-of-phosphorylation, S→D mimics constitutive phosphorylation (pg 4, lines 25-32). Furthermore, the specification discloses that the physiological relevance is not known for many sites of phosphorylation. Thus, the special technical feature caused by a given amino acid substitution at any site of post-translational modification encompassed by the claims cannot be predicted *a priori*. Applicants are also reminded that nucleic acid sequences encoding different proteins, and the amino acid sequences they encode, are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleic acid and amino acid sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq.

With respect to ii-iii), the instantly claimed cell types species are common technical features that do not contribute over the prior art because the art has long recognized the ability of the recited cell type species to be adequate hosts for a vector, e.g. providing an adequate environment in which the vector can reproduce itself. Applicant has provided no evidence that the instantly claimed vector and host cells possess an essential, special technical feature that restricts host cell compatibility so as to distinguish and contribute the vector and the corresponding host cell over the prior art.

It is noted that should Applicant traverse the species election requirement, that Applicant was invited to submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. Applicant has not done so.

MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to methods of treating disease, methods of synthesizing a protein, transgenic animals, and methods for identifying compounds requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to methods for identifying compounds would not be adequate to uncover prior art related to transgenic animals.

Further, a search and examination of all the claims directed to both embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claims including limitations to methods of treating disease, methods of synthesizing a protein, transgenic animals, and methods for identifying compounds in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 5-7, 9, 11-16, 18-19 and 21-23 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1-4, 8, 10, 17 and 20 are under consideration.

Priority

5. This application is a 371 of PCT/EP03/14016, filed December 10, 2003. Applicant's claim for the benefit of a prior-filed application PCT/EP03/14016, filed December 10, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). A certified copy of EPO 020286578.1, filed December 20, 2002 is filed with the instant application. .

Accordingly, the effective priority date of the instant application is granted as December 20, 2002.

Information Disclosure Statement

. Applicant has filed an Information Disclosure Statement on September 12, 2005 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Drawings

Sequence compliance

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by

"SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers.

Applicant's attention is drawn, in particular, to the following locations in the instant specification: Figure 4(b).

Sequences must be assigned a SEQ ID NO. Sequences must be provided in computer readable format (CRF) and on paper. Further, a statement indicating the two formats are the same must also be provided.

See attached Notice to Comply.

The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Specification

The disclosure is objected to because of the following informalities: the specification discloses that TIF-IAS649D both activates Pol I transcription and represses Pol I transcription (pg 41, lines 29-32).

Clarification and/or correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. **Claims 1-4 are rejected under 35 U.S.C. 101** because the claimed invention is directed to non-statutory subject matter. In *Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980), the Supreme Court set forth several tests for weighing whether patentable subject matter under 35 U.S.C. 101 is present, stating that:

"The relevant distinction was not between living and inanimate things but between products of nature, whether living or not, and human-made inventions. [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter."

The claims, as written, does not sufficiently distinguish a nucleic acid encoding an inactive form of TIF-IA as it exists naturally, e.g. prior to ERK-mediated phosphorylation stimulated by extracellular signals or natural genetic variants in a population, because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the "hand of man", the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" before nucleic acid molecule. See MPEP 2105. Furthermore the scope of invention as claimed embraces a genetically modified human carrying in its genome or at least some of their cells a recombinant genetic material. It is USPTO policy not to allow claims to humans (1077 O.G. 24 April 1987).

Appropriate correction is required.

7. **Claims 1-4, 8, 10, 17 and 20 are rejected under 35 U.S.C. 101** because the claimed invention is not supported by either a specific and substantial utility.

According to the Revised Utility Examination Guidelines (see the Federal Register, Vol. 66, No. 4, pp. 19092-1099; January 5, 2001; also available at http://uspto.nov/web.menu.utility.pdf) the following definitions of specific, and substantial apply.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility. See also MPEP 2107-2107.02, and *Brenner Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

Specific Utility

A "specific utility" is specific to the subject matter claimed and can "provide a well-defined and particular benefit to the public." *In re Fisher*, 421 F.3d 1365, 1371, 76 USPQ2d 1225, 1230 (Fed. Cir. 2005). This contrasts with a *general* [emphasis added] utility that would be applicable to the broad class of the invention.

Substantial Utility

"[A]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the substantial utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Fisher*, 421 F.3d at 1371, 76 USPQ2d at 1230.

In the instant case, the specification contains assertions that the claimed invention, nucleic acid molecules encoding TIF-IA mutations that are inactive and have no, or not complete, post-translational modification "opens up the possibility" to produce cell lines or transgenic non-human animals with an inactive TIF-IA (pg 18, lines 26-29), wherein said transgenic animal may be useful in the development of therapies or treatment for diseases caused by aberrant expression of a TIF-IA protein or associated with increased cell proliferation, e.g. tumor (pg 19, lines 12-16), the study of dominant-negative effects of inactive TIF-IA (pg 19, line 23), or the screening and pharmacological study of drugs (pg 20, line 2).

The specification does not support a credible, specific and substantial utility because the specification does not teach a relationship of TIF-IA, mutant or otherwise aberrant from wildtype conditions, to any specific disease, or establish any involvement of TIF-IA in the etiology of any specific disease. The specification asserts that the claimed polypeptides are involved in cell proliferation, but Schnapp et al (EMBO J 9: 2857-2863, 1990) teach that "regulation of cell proliferation is a complex process" involving a multitude of proteins. While cell cycle progression is impaired in vitro when a cell is expressing the TIF-IA S649A mutation, the cells remain viable (pg 42-43, Example 7). The specification does not disclose a correlation between any specific proliferative disorder and an altered level or form of the claimed polynucleotides or polypeptide encoded by the claimed invention. For example, the specification does not show whether the claimed polynucleotides or polypeptides encoded by the claimed invention is over-expressed or under-expressed in a specific, diseased tissue compared to the healthy tissue control. Furthermore, these utilities are not specific to the claimed invention because such cell lines and transgenic animals may comprise any one of an enormous genus of structurally distinct nucleic acid sequence encoding mutant TIF-IA polypeptides.

The disclosed utilities are not considered credible, specific and substantial because they are just invitations for one skilled in the art to figure out how the protein functions or what the biological activities are for the claimed invention, clearly indicated by the phrase "opens up the possibility". While methods of researching a disease state [potentially] caused by the expression of a mutant human TIF-IA polypeptide in a transgenic cell or organism, and screening or pharmacological studies of drugs affecting TIF-IA are of value to the scientific and medical arts, this use is not considered a specific, substantial or practical utility because it does not provide some "real-world" value or immediate benefit to the public. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Basic research, such as studying the properties of the claimed TIF-IA product itself, or the mechanisms in which the human TIF-IA is involved, does not define "substantial utilities". Labels such as "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out how to use it for

themselves. The instant application has failed to provide guidance as to identity of all of the amino acids necessary for post-translational modification, e.g. phosphorylation, glycosylation, methylation and acetylation of human TIF-IA, and how one of skill in the art could use the claimed invention of nucleic acids encoding mutant human TIF-IA in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson,* 148 USPQ at 696.

8. **Claims 1-4, 8, 10, 17 and 20 are also rejected under 35 U.S.C. 112, first paragraph.** Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility for the reasons set forth above, one skilled in the art clearly would not know **how to use** the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **Claim 1-4, 8, 10, 17 and 20 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a nucleic acid molecule encoding an inactive form of the human transcription initiation factor TIF-IA, wherein said TIF-IA is not, or not completely, post-translationally modified. At issue for the purpose of written description requirements are the identities of those amino acids necessary for the *complete* [emphasis added] post-translational modification of TIF-IA and their corresponding effects on TIF-IA activity, specifically inactive vs. active states, when mutated. When the claims are analyzed in light of the specification, instant invention recites/encompasses an enormous genus of structurally distinct nucleic acids encoding an inactive form of the human TIF-IA polypeptide, wherein the mutant proteins are not, or not completely post-translationally modified, e.g. phosphorylation, glycosylation, methylation and acetylation.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). In the instant case, the specification discloses only Serines 44, 199, 633 and 649 of human TIF-IA that are post-translationally modified by phosphorylation.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the introduction of single point mutation(s), e.g. insertion, deletion and/or amino acid substitution, at

positions where a post-translational modification of the amino acid sequence, e.g. glycosylation, methylation, acetylation or phosphorylation, influences particular properties (pg 15, lines 2-6; pg 16, lines 5-12). The specification defines the term "inactive form" as any version of TIF-IA which as completely or partially lost its capability to initiate RNA Polymerase I transcription (pg 14, lines 13-16). These versions comprise TIF-IA molecules containing substitution(s), deletion(s) and/or insertions of one or more amino acids rendering the molecule inactive and include TIF-IA which, *in vivo*, can no longer be modified in such a way that an inactive pre-form is converted into an active form (pg 14, lines 13-21). However, the specification does not disclose the objective, quantifiable units by which TIF-IA activity is to be determined "completely" as opposed to "partially" active.

However, TIF-IA is phosphorylated at multiple sites, the physiological relevance of most of them is not known (pg 4, lines 20-21). Furthermore, the specification does not disclose the identity of those amino acids responsible for each and every TIF-IA post-translational modification, nor provides a nexus between each TIF-IA post-translational modification, e.g. phosphorylation, glycosylation, methylation **and** acetylation, and the active or inactive TIF-IA status. It is noted that all these TIF-IA mutant alleles vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The applicant has not provided any description or reduction to practice of the enormous genus of nucleic acid molecules encoding inactive forms of human TIF-IA, wherein said inactive forms of human TIF-IA are not, or not completely, post-translationally modified. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the nucleotide sequences which encode human TIF-IA that are not [completely] phosphorylated, glycosylated, methylated and/or acetylated as defined by the specification or encompassed by the

claims. The four mutant species specifically disclosed, Serines 44, 199, 633 and 649 of human TIF-IA that are post-translationally modified by phosphorylation, is not representative of the genus of post-translational modifications because the genus is highly variant. Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of nucleic acid molecules encoding inactive forms of human TIF-IA, wherein said inactive forms of human TIF-IA are not, or not completely, post-translationally modified, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. **Claims 1-4, 8, 10, 17 and 20 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for making a nucleic acid molecule encoding the human transcription initiation factor TIF-IA, wherein the serine residue at position 649 is replaced by an alanine residue, a recombinant vector containing said nucleic acid molecule, and an isolated recombinant host cell line which contains said recombinant vector, does not reasonably provide enablement for making an enormous genus of structurally distinct nucleic acids encoding inactive forms of TIF-IA, wherein said inactive forms of TIF-IA are not, or not completely, post-translationally modified, nor for using a pharmaceutical composition comprising a nucleic acid molecule encoding the genus of inactive forms of the human transcription initiation factor TIF-IA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets

the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing an enormous genus of structurally distinct nucleic acids encoding an inactive form of the human TIF-IA polypeptide, wherein the mutant proteins are not, or not completely post-translationally modified, e.g. phosphorylation, glycosylation, methylation and acetylation.

The inventive concept of the instant application is the identification of Serine 649 that, when mutated to an alanine (S649A), renders the TIF-IA polypeptide inactive. Applicant contemplates that the administration of nucleic acid molecules encoding said mutation may be useful as a pharmaceutical composition.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification discloses that TIF-IA is phosphorylated at multiple sites; however, the physiological relevance of most of them are not known, and the respective protein kinases yet need to be identified. Serum stimulation achieves the phosphorylation of TIF-IA peptides (pg 38, Example 5), wherein said peptides may be phosphorylated by ERK-dependent kinases directly or indirectly. Phosphoamino acid analysis established that TIF-IA is exclusively phosphorylated on serine residues (pg 39, lines 11-12). The Ras-ERK pathway targets S649 and S633 within the C-terminal tail of TIF-IA, wherein respective S→A mutants are transcriptionally inactive and

impair cell growth (pg 4, lines 20-29). S649A mutations suppress RNA Pol I transcription in cell extracts *in vitro* and in transfected cells (pg 41, lines 19-34).

Based upon these observations, Applicant contemplates the introduction of single point mutation(s), e.g. insertion, deletion and/or amino acid substitution, at positions where a post-translational modification of the amino acid sequence, e.g. glycosylation, methylation, acetylation or phosphorylation, influences particular properties (pg 15, lines 2-6; pg 16, lines 5-12). The specification defines the term "inactive form" as any version of TIF-IA which as completely or partially lost its capability to initiate RNA Polymerase I transcription (pg 14, lines 13-16). These versions comprise TIF-IA molecules containing substitution(s), deletion(s) and/or insertions of one or more amino acids rendering the molecule inactive and include TIF-IA which, *in vivo*, can no longer be modified in such a way that an inactive pre-form is converted into an active form (pg 14, lines 13-21). However, the specification does not disclose the objective, quantifiable units by which TIF-IA activity is to be determined "completely" as opposed to "partially" active so as to inform the artisan whether or not the claimed subject matter has been infringed.

Applicant contemplates a genus of vectors containing the nucleic acid molecules of the invention (pg 17, lines 14-29; pgs 21-22, joining ¶), and a genus of host cells transformed or transfected with said vectors (pgs 17-18, joining ¶).

Because cell growth and proliferation is regulated by a variety of extracellular signals, and the proliferation of cells can be inhibited by the introduction of the S649A TIF-IA allele, Applicant contemplates the nucleic acid molecule may be useful in the development of therapies or treatment for diseases caused by aberrant expression of a TIF-IA protein or associated with increased cell proliferation, e.g. tumor (pg 19, lines 12-16). Thus, the present invention also relates to a pharmaceutical composition comprising a nucleic acid molecule encoding a TIF-IA polypeptide, a vector encoding said nucleic acid molecule, and a pharmaceutically acceptable excipient, diluent or carrier (pg 20, lines 12-16).

The specification discloses that S649 is *essential* [emphasis added] for TIF-IA function in cellular pre-rRNA synthesis (pg 41, lines 3-35; Figure 5). The basis for Applicant's assertion of "essential" is unclear, because use of term 'essential' implies that cellular pre-rRNA synthesis

cannot occur in the absence of active TIF-IA. However, cellular pre-rRNA synthesis is clearly detectable, and thus, if the TIF-IA S649A mutation renders the transcription initiation factor "inactive" as claimed, then one of ordinary skill in the art would reasonably expect to see no transcripts in the host cell expressing the mutant TIF-IA polypeptide (e.g. Figure 5C). Furthermore, while cell cycle progression is impaired *in vitro* when a cell is expressing the TIF-IA S649A mutation, the cells remain viable and continue proliferating (pg 42-43, Example 7), indicating that cellular pre-rRNA synthesis is not completely inhibited.

While Applicant contemplates the entire genus of post-translational modifications of TIF-IA, the specification does not disclose the *complete* [emphasis added] post-translationally modified form of the TIF-IA polypeptide that is/are active, the identity of those amino acids responsible for each and every post-translational modification, nor provides a nexus between each TIF-IA post-translational modification, e.g. phosphorylation, glycosylation, methylation **and** acetylation, and the active or inactive TIF-IA status. Even within the post-translational modification subgenus of phosphorylation, the instant specification discloses only some (not all) serine residues that are phosphorylated and their corresponding effects on TIF-IA transcription promotion activity.

The specification is also silent with respect to the ability of transfected TIF-IA S649A to inhibit cell proliferation in tumorigenic cells, *in vitro*, *ex vivo* or *in vivo*. There are no working examples teaching the administration of a pharmaceutical composition comprising the TIF-IA S649A allele to a subject in need of therapeutic treatment of tumors.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The instant invention encompasses the fields of molecular biology, cell biology and gene therapy, wherein the level of skill of the ordinary artisan is considered to be high.

The claimed nucleic acids encompass an enormous genus of structurally distinct nucleic acids encoding an inactive form of the human TIF-IA polypeptide, wherein the mutant proteins are not, or not completely post-translationally modified, e.g. phosphorylation, glycosylation, methylation and acetylation. However, the pre- and post-filing art is silent with respect to each

and every post-translational modification of TIF-IA, which amino acids are responsible for the corresponding post-translational modifications, and which post-translational modification(s) will necessarily yield an inactive TIF-IA polypeptide when the amino acid residue(s) is mutated.

The art teaches that bacterially expressed TIF-IA, which should not contain post-translational modifications of eukaryotes, e.g. proper phosphorylation, is as efficient *in vitro* as endogenous (eukaryotic) TIF-IA to establish transcriptional activity (Fath et al, PNAS, 98(25): 14334-14339, 2001; pg 14337, col. 1, "Rrn3p...Nonphosphorylated Form" to pg 14338, col. 1, lines 1-3). Furthermore, Moorefield et al (PNAS 97(9): 4724-4729, 2000; *of record in IDS) teach a polynucleotide encoding amino acids 1-587 (absence of amino acids 588-651) of human TIF-IA (pg 4726, Figure 1), wherein said polypeptide lacks eight C-terminal serine residues, including Serine 649 disclosed in the instant specification to be functionally important and phosphorylated by ERK and RSK (pg 3, line 35). While this TIF-1A C-terminal truncation mutation clearly is not completely post-translationally modified (as compared to the wildtype TIF-IA polypeptide), Moorefield et al teach that this C-terminal deletion mutation provides cell viability at all temperatures tested, and thus is functional (pg 4727, col. 1). Therefore, a discrepancy exists between the disclosure in the instant specification and the teachings of the prior art regarding those mutations yielding TIF-IA polypeptides that are not completely post-translationally modified and either retain biological function or are inactive.

Applicant contemplates that the recombinant nucleic acid composition may be introduced *in vivo*, and thus Applicant's invention falls within the realm of gene therapy, which is in the nature of transforming cells with nucleic acids encoding therapeutic molecules to produce a therapeutic effect.

However, as discussed above, Applicant only discloses working examples of the invention using *in vitro* cell culture conditions. The *in vitro* experimental data presented is clearly not drawn to subjects with cancer cells. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma 9:1-25, 1993) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in*

vivo cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract).

Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Tian et al (Physiol Genomics, 17: 170-182, 2004) teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Similarly, Van Dyke et al (Cancer Genetics and Cytogenetics 241: 137-141, 2003) teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and pg 140, col. 1, last two paragraphs before acknowledgments). Zaslav et al (Amer J Medical Genetics 107: 174-176, 2002) teach that prenatal mosaicism for a deletion of chromosome 10 (q23) is rare, and that most diagnosed deleted (10q) mosaicism represents culture artifact, i.e. diagnosed individuals may have a deletion at this site when their isolated cells were grown in tissue culture or subjected to low folate conditions (abstract, and p. 175, first column, paragraph under Discussion). Kunkel et al (Neuro-oncology 3(2): 82-88, 2001) teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the *in vivo* situation, and most likely represents a culture artifact (abstract).

The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, artifactual chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays.

One of ordinary skill in the art recognizes that *in vitro* conditions do not reasonably extrapolate to *in vivo* conditions because for *in vitro* methods, an artisan has significantly greater control over access to a chosen cell type and the ability to optimize the amount of, and the means

by which, the recombinant nucleic acid is delivered to the chosen cell population, which are not identically transferable to *in vivo* conditions. Rather, for *in vivo* methods, an artisan must consider method steps to optimally deliver a therapeutically effective amount of the recombinant nucleic acid to the chosen cell, organ or tissue type, e.g. nerve cells, endothelial cells, hematopoietic cells, muscle, brain, liver, heart, colon, pancreas, kidney, etc, wherein each chosen cell, organ or tissue type demands distinctly different, non-identical cell biological and physiological considerations, e.g. route of administration, to achieve the necessary incorporation of the recombinant nucleic acid and effect the desired therapeutic result.

With regard to gene therapy, at the effective filing date of the present application, May 17, 2002, the attainment of any therapeutic effect via gene therapy was, and remains, highly unpredictable, let alone for the attainment of prophylactic effects via gene therapy mechanisms as contemplated by Applicants. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. There are several known factors that limit an effective human gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells. For example, Deonarain (Deonarain, M., Expert Opin. Ther. Pat. 8: 53-69, 1998) indicates that:

> "[O]ne of the biggest problems hampering successful gene therapy is the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (page 65, CONCLUSION). Verma and Somia (Nature 389: 239-242, 1997) review vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that:

"the Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression . . ."

The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3). Even in 2005, Verma and Weitzman (Annu. Rev. Biochem. 74:711-738, 2005) still state:

"The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to head disease and cancer. It has, therefore, generated great hopes and great hypes, but it has yet to deliver its promised potential", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, gene therapy will be added to our medicinal armada and the ever- expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph).

Goncalves (BioEssays 27:506-517, 2005) also states:

"Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph).

Gardlik et al. (Med. Sci. Monit. 11:RA110-121, 2005) conclude:

"Although clinical trials have already started, there are still numerous limitations that must be solved before routine clinical use. Nevertheless, it can be expected that future research will bring tissue- and disease-specific delivery strategies and that this hurdle will be overcome at last" (page RA119, right-hand column, last paragraph).

Thus, the art recognizes significant obstacles and unpredictability for an artisan to achieve optimal *in vivo* efficiency for targeting of the inventive recombinant nucleic acid to a chosen cell, tissue or organ type, optimal *in vivo* efficiency for gene transfer of the inventive recombinant nucleic acid, and optimal *in vivo* efficiency to achieve effective expression levels of the mutant TIF-IA molecule, for long enough periods to effect the therapeutic results.

The state of the art as applied to the understanding of how TIF-IA activity is regulated, e.g. by post-translational modification in response to signal transduction molecules, is, at the time of filing of the instant application, in its infancy. Thus, it follows that the technology of using any inactive form of TIF-IA for therapeutic purposes is also in its infancy. The art recognizes that TIF-IA activity is regulated by diverse signals that affect signal cell metabolism and growth, and the determination of all modified residues in TIF-IA in dependency of their functional state will provide an important tool to understand the basic mechanism of ribosomal DNA transcription and will contribute to the knowledge of how transcriptional regulation is coupled to growth control of the cell (Fath et al, pg 14339, col. 2, last ¶). In particular, the complexity of the phosphorylation pattern of TIF-IA is not surprising. The dissection of the different signaling pathways and their effects on TIF-IA function will be a major challenge for future investigations (Zhao et al, Mol. Cell 11:405-413, 2003; *of record in IDS, pgs 411-412, joining ¶). Thus, the art recognizes considerable uncertainty regarding the nexus between TIF-IA structure, post-translational modifications and function, and continued experimentation is required to achieve the desired understanding.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate which amino acids are responsible for the complete post-translational modification, e.g. phosphorylation, glycosylation, methylation **and** acetylation of human TIF-IA, and which of the enormous genus of undisclosed amino acid substitutions, deletions and/or insertions will yield inactive forms of human TIF-IA

that are not, or not completely post-translationally modified, e.g. so as to be useful in a pharmaceutical composition to achieve a clinically relevant, therapeutically effective result. The prior art is silent regarding all of the post-translational modifications and their corresponding effect(s) on TIF-IA activity embraced by the claims, and thus the instant specification is required to disclose specific, not general, instruction to the artisan as to which amino acids may be altered so as to synthesize the claimed polypeptide(s) having the claimed functions, e.g. therapeutically efficacy. However, the specification fails to disclose this necessary information.

Further, it is noted that a when a composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use. In this case, the specification must teach enablement of a pharmaceutical use since the claim recites a pharmaceutical composition. According to Steadman's Medical Dictionary (24th Edition, 1982), "pharmaceutical" means "relating to pharmacy or to pharmaceutics". In the same dictionary, "pharmacy" is defined as: 1. The practice of preparing and dispensing drugs. 2. A drugstore. **Clinical p.,** a branch of p. practice that emphasizes the therapeutic use of drugs rather than the preparation and dispensing of drugs. Thus, broadly speaking, "a pharmaceutical use" would be one wherein something is being used as a "drug". Further, Steadman's Medical Dictionary (24th Edition, 1982) defines "drug" as "A therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Likewise, Ansel et al (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body." Considering all of this, a good definition for "a pharmaceutical use" would be any use, other than as food, wherein a substance is used on or in the body to prevent, diagnose, alleviate, treat, or cure a disease in humans or animals. The following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for *in vivo* imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection).

To enable a pharmaceutical use for a substance, the specification must teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation,

treatment, or cure a disease in the animal to which the substance is administered. However, the instant specification does not indicate any prevention, diagnosis, alleviation, treatment or cure of any of disease or condition in an animal to which the pharmaceutical composition comprising a nucleic acid sequence encoding an inactive form of the human transcription initiation factor TIF-IA, wherein the serine residue at position 649 is replaced by an alanine residue is administered. While Applicant may contemplate a pharmaceutical use for the claimed pharmaceutical composition (pg 20, lines 10-16), the specification must enable a pharmaceutical use. In this case, the facts tell us that such a use is not enabled. Administering the inventive nucleic acid molecule to isolated cells *in vitro* to slow cell proliferation does not provide enablement for the claim because using the compound merely to ascertain the effect of the mutated nucleic acid is not a pharmaceutical use. The pharmaceutical use must occur within the animal to which the inventive nucleic acid is administered for the prevention, diagnosis, alleviation, treatment, or cure of disease.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. The specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a nucleic acid molecule encoding the human transcription initiation factor TIF-IA, wherein the serine residue at position 649 is replaced by an alanine residue, a recombinant vector containing said nucleic acid molecule, and an isolated recombinant host cell line which contains said recombinant vector, is proper. The specification shows how to make the claimed nucleic acid molecule; however, the specification is not enabled for **how to use** the claimed nucleic acid molecule.

Note: such a rejection as it pertains to pharmaceutical use could be overcome by deleting the word "pharmaceutical" from the claim. It is noted that when no use is recited in a claim, any enabled use will suffice.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. **Claims 1-4, 8, 10, 17 and 20 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "inactive" and "not completely" in claim 1 are relative terms which render the claims indefinite. The terms "inactive" and "not completely" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The specification discloses that inactive forms of TIF-IA have lost, completely or partially, the ability to initiate Pol I transcription, wherein the TIF-IA molecules comprise one or more amino acid substitutions, deletions and/or insertions rendering the TIF-IA molecule inactive such that it can no longer be modified *in vivo* in such a way that an inactive pre-form may be converted into an active form, wherein such modifications include phosphorylation, glycosylation, methylation and acetylation (pg 14, lines 14-22).

However, the specification does not disclose the objective, quantifiable units by which TIF-IA activity is to be determined "completely" as opposed to "partially" active so as to inform the artisan whether or not the claimed subject matter has been infringed.

The specification also does not disclose the *complete* [emphasis added] post-translationally modified form of the TIF-IA polypeptide that is completely active. The specification provides no nexus between each post-translational modification of TIF-IA, including phosphorylation, glycosylation, methylation and acetylation, and the active or (partially) inactive TIF-IA form(s).

Dependent claims are included in the basis of the rejection because although they recite and encompass inactive forms of TIF-IA that are "not completely post-translationally modified", they do not clarify the nature of complete post-translational modification(s) of TIF-IA and inactivity.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. **Claims 1 and 17 are rejected under 35 U.S.C. 102(b)** as anticipated by Moorefield et al (PNAS 97(9): 4724-4729, 2000; *of record in IDS).

With respect to Claim 1, Moorefield et al teach a nucleic acid encoding a human TIF-IA polypeptide, wherein said polypeptide is truncated at the carboxy-terminus (absence of amino acids 588-651) and lacks eight C-terminal serine residues, including Serine 649 disclosed in the instant specification to be phosphorylated by ERK and RSK (pg 3, line 35), said polypeptide further comprising the mutation L136P (pg 4727, col. 2), wherein said mutation renders the polypeptide inactive and temperature-sensitive. Moorefield et al do not teach the inactive polypeptide to be not, or not completely post-translationally modified. However, absent evidence to the contrary, the L136P TIF-IA fulfills the instant functional limitations in that the polypeptide is inactive and it is not completely post-translationally modified due to the C-terminal deletion (Specification, pg 14, lines 33-36 to pg 15, lines 1-2).

With respect to Claim 17, Moorefield et al teach the cell line comprising the nucleic acid molecule of Claim 1 to be the prokaryotic bacterial strain *Eschericia coli* (for cloning) and the eukaryotic yeast *Saccharomyces cerevisiae* (expression and functional studies) (pg 4725, Methods).

13. **Claims 1 and 17 are rejected under 35 U.S.C. 102(a)** as being anticipated by Yuan et al (EMBO 3(11): 1082-1087, 2002; available online October 22, 2002, *of record in IDS).

With respect to Claim 1, Yuan et al disclose mutations of human TIF-IA (pg 1086, col. 1, Plasmids), wherein deletion 377-512 removes several serine residues, including conserved Serine 409 and Serine 497, and a domain that serves an essential role in the pre-initiation complex assembly (pg 1085, col. 2, Figure 3).

Yuan et al do not teach the inactive polypeptide to be not, or not completely post-translationally modified. However, absent evidence to the contrary, the deletion mutant TIF-IA fulfills the instant functional limitations in that the polypeptide is inactive and it is inherently not completely post-translationally modified due to the loss of conserved, and other, serine residues (Specification, pg 14, lines 33-36 to pg 15, lines 1-2).

With respect to Claim 17, Yuan et al teach the cell line comprising the nucleic acid molecule of Claim 1 to be the eukaryotic insect cells Sf9 (pg 1085, Figure 3).

14. **Claims 1, 17 and 20 are rejected under 35 U.S.C. 102(e)** as being anticipated by Reeder et al (U.S. Patent No. 6,825,034 B2).

With respect to Claim 1, Reeder et al contemplate human Rrn3 (also known as TIF-IA) polypeptide derivatives including those altered by substitution, addition or deletion of one or more amino acid residues that lack a desired Rrn3 property of interest (col. 18, lines 10-25), wherein said derivatives are differentially modified, e.g. phosphorylation (col. 19, lines 39-45).

With respect to Claim 17, Reeder et al contemplate cell lines, wherein the nucleic acid is stably transferred to a cell so that the nucleic acid is expressible by the cell and is heritable and expressible by the cell progeny (col. 28, lines 50-53), e.g. mammalian host cell strains (col. 17, lines 35-62).

With respect to Claim 20, Reeder et al contemplate the administration of nucleic acids encoding Rrn3 variants for use in treating disorders involving cell proliferation, e.g. tumorigenesis, by altering Rrn3 function (col. 25, lines 10-45), wherein the nucleic acid

composition further comprises a pharmaceutically acceptable excipient, diluent or carrier (col. 34, lines 13-53).

Conclusion

15. No claims are allowed. Claims 2-4, regarding the limitation wherein the serine residue at position 649 of human TIF-IA is replaced with alanine, are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kevin K. Hill

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Notice to Comply	Application No. 10/539,473	Applicant(s) Grumm et al	
	Examiner Kevin K. Hill	Art Unit 1633	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequences set fort in the specification and drawings lack sequence identifiers, specifically: Figure 4b.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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